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09/830,144	04/20/2001	Masayuki Tsuchiya	06501-076001	9796

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/830,144	TSUCHIYA ET AL.
	Examiner	Art Unit
	Sheridan L. Swope	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-67* is/are pending in the application.

4a) Of the above claim(s) *12-26,28-40 and 61-67* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-11,27 and 41-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0703* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's response, on August 27, 2003 to the first Office Action on the Merits of this case is acknowledged. It is acknowledged that applicants have cancelled Claim 1, amended Claims 2-11, and added Claim 41-67. Claims 2-67 are pending. Claims 12-26, 28-40, and 61-67 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 2-11 and 27 are hereby reconsidered and Claims 41-60 are considered.

Specification-Objections

The specification is objected to because the "Brief Description of the Drawings" section is not in the proper location within the specification. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of Claims 2-11 and 27 under 35 U.S.C. 112, first paragraph for lack of enablement is maintained, while Claims 41-47, 49, 50, and 54-60 are rejected under 35 U.S.C. 112, first paragraph for lack of enablement. The specification is enabling for a method of screening for compounds that inhibit the binding of the TAK1 set forth by residues 76-303 of SEQ ID NO: 2, or variants thereof comprising 1-20 or 1-10 altered amino acid residues or variants thereof that hybridize under high stringency conditions with residues 408-1091 of SEQ ID NO: 1 with a TAB1 set forth by residues 437-504 of SEQ ID NO: 4, or variants thereof that hybridize under high stringency conditions with residues 1338-1541 of SEQ ID NO: 3. However, the specification does not reasonably provide enablement for methods of screening for compounds that inhibit the binding of said TAK1 fragments and variants of TAB1 wherein the variants comprise 1-20 or 1-10 altered amino acid residues in 437-504 of SEQ ID NO: 4. The specification does not enable any person skilled in the art to which it pertains, or with which it is

most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 2-11, 27, 41-47, 49, 50, and 54-60 are so broad as to encompass methods of screening for compounds that inhibit the binding of the TAK1 set forth by residues 76-303 of SEQ ID NO: 2, or a variants thereof that bind TAB1 and have either 1-20 amino acid residues altered or that hybridize under high stringency conditions with residues 408-1091 of SEQ ID NO: 1 with TAB1 variants having 1-20 or 1-10 altered amino acid residues altered in 437-504 of SEQ ID NO: 4. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of TAB1 proteins broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired TAK1/TAB1 binding activity requires a knowledge of and guidance with regard to which amino acids in the proteins' sequences, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structures relate to the binding function. However, in this case the enablement of the disclosure is limited to the TAB1 set forth by SEQ ID NO: 4, the fragment thereof comprising residues 437-504 of SEQ ID NO: 4, any variant of said fragment having one or two residues changed, or any variant of said fragment wherein the polynucleotide encoding the variant hybridizes to SEQ ID NO: 3 under high stringency conditions.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims,

and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the Claims 2-11, 27, 41-47, 49, 50, and 54-60, which encompasses methods of screening for compounds that inhibit the binding of the TAK1 set forth by residues 76-303 of SEQ ID NO: 2, or a variants thereof that bind TAB1 and have either 1-20 amino acid residues altered or that hybridize under high stringency conditions with residues 408-1091 of SEQ ID NO: 1 with TAB1 variants having 1-20 or 1-10 amino acid residues altered in residues 437-504 of SEQ ID NO: 4. The specification does not support the broad scope of Claims 2-11, 27, 41-47, 49, 50, and 54-60 because the specification does not establish: (A) regions of the TAB1 set forth by residues 437-504 of SEQ ID NO: 4 which may be modified without effecting the binding activity; (C) the general tolerance of the binding activity to modification of the TAB1 set forth by residues 437-504 of SEQ ID NO: 4 and the extent of such tolerance; (D) a rational and predictable scheme for modifying any residues within the TAB1 set forth by residues 437-504 of SEQ ID NO: 4 with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices of variant TAB1 proteins is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope

of the claims broadly including methods of screening for compounds that inhibit the binding of the TAK1 set forth by residues 76-303 of SEQ ID NO: 2, or a variants thereof that bind TAB1 and have either 1-20 amino acid residues altered or that hybridize under high stringency conditions with residues 408-1091 of SEQ ID NO: 1, with TAB1 variants having 1-20 or 1-10 amino acid residues altered in residues 437-504 of SEQ ID NO: 4. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 2-11, 27, and 41-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for testing the effect of inhibitors of TAK1/TAB1 binding on TGF- β-induced expression of inflammatory cytokines, does not reasonably provide enablement for testing the effect of inhibitors of TAK1/TAB1 binding on expression of inflammatory cytokines in response to any activator. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 2-11, 27, and 41-60 are so broad as to encompass testing the effect of inhibitors of TAK1/TAB1 binding on expression of inflammatory cytokines in response to any activator, including specifically IL-1 and TNF. The scope of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of activators of expression of inflammatory cytokines broadly encompassed by the claim. Since the signal

transduction mechanism of an activator determines which intracellular molecules are important for the biological response, predictability of which changes in intracellular signaling will affect the biological response requires a knowledge of and guidance with regard to which molecules and signaling events, if any, are affected by a specific inhibitor and which are tolerant of modification, and detailed knowledge of the ways in which the signaling molecule relates to its function. As pointed out by applicants, " A mere disclosure that TAKI kinase activity can be induced by addition of 1L-1 does not suggest that TAB 1 binding is involved in this induction, nor that the TAKI activity induced by 1L-1 is linked to expression of inflammatory cytokines. Without this insight, there would have been no reason to carry out the screening method set forth in claims 41 and 27, as amended." In fact, an inhibitor of TAK1/TAB1 binding does not affect activation of TAK1 by IL-1 and TNF (Shirakabe et al, 1997, p8143, parg 3, lines 7-12). Thus, in this case, enablement by the disclosure is limited to testing the effect of inhibitors of TAK1/TAB1 binding on TGF-β-induced expression of inflammatory cytokines.

While molecular methods for testing the effects of compounds on signal transduction mechanisms and biological responses to activators are known in the art, it is not routine in to use inhibitors useful in one assay in another assay wherein said inhibitor would be predicted not to work. Therefore, assays to test for inhibition of a cellular response, using a blocker of a specific intracellular signaling step, which can be performed with a reasonable expectation of success in obtaining the desired inhibition of the cellular response using said blocker, and the results of such testing are unpredictable.

The specification does not support the broad scope of the Claims 2-11, 27, and 41-60 which, encompasses testing the effect of all inhibitors of TAK1/TAB1 binding on the expression

of inflammatory cytokines induced by any activator. The specification does not support the broad scope of Claims 2-11, 27, and 41-60 because the specification does not establish (A) which activators of inflammatory cytokine expression act through TAK1/TAB1 binding; (B) the general tolerance of the induction of inflammatory cytokine expression by any activator to inhibition of TAK1/TAB1 binding; and (C) the specification provides insufficient guidance as to which of the large number of possible compounds and treatments that induce expression of inflammatory cytokines is likely to be successfully inhibited by an agent that blocks TAK1/TAB1 binding.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including testing the effect of inhibitors of TAK1/TAB1 binding on expression of inflammatory cytokines in response to any activator. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request for withdrawal of the rejection of Claims 1-11 and 27 under 35 U.S.C. 112, first paragraph, for lack of enablement, applicants provide the following arguments, which are also relevant to new Claims 41-47, 49, 50, and 54-60.

(1) "Claims 41, 61, 63, and 67 also specify that the TABI protein either comprise amino acids 437 to 504 of SEQ ID NO:4 (specification at page 11, lines 7 to 9); bind a TAKI and comprise

amino acids 437 to 504 of SEQ ID NO:4, with one or more (up to 20) amino acid substitutions, deletions, and/or additions (specification at page 11, lines 16-20), or be encoded by a DNA sequence that hybridizes to the complement of nucleotides 1338 to 1541 of SEQ ID NO:3 under washing conditions of 42°C, 5 x SSC, 0.1% sodium dodecyl sulphate, and 50% formamide (specification at page 12, line 35, to page 13, line 24). ... In addition, Reference Example 1 of the specification (page 54, line 1) discloses a TABI fusion protein that includes the C-terminal 68 amino acid residues of TABI fused with the transcription activation domain of VP16. Other specific examples of TAB 1 proteins are provided in the specification at page 8, line 29, to page 9, line 2 and page 9, lines 10 to 35. Additional information regarding TABI proteins is set forth in the specification at page 11, line 7, to page 12, line 9."

(2) "Regarding predictability (see item (D) in the quotation from the Office Action), the prior art generally teaches that "proteins are surprisingly tolerant of amino acid substitutions" (see page 1306, second column, first full paragraph of Bowie et a1., 1990, "Deciphering the message in protein sequences: tolerance to amino acid substitutions," Science 247:1306-1310, copy attached). Based on the teachings of Bowie et al., one would expect to find that over half (and possibly well over half) of random substitutions in any given protein would result in a protein with full or nearly full activity. This concept is also addressed in the specification at page 9, lines 2 to 9, which states [I]t has been already known that a peptide having an amino acid sequence that is modified by one or more amino acid substitutions, deletions, and/or additions in a amino acid sequence is still capable of having its original biological activity (Mark, D. F. et a1., Proc. Natl. Acad. Sci. USA (1984) 81, 5662-5666, Zoller, M. J. & Smith, M. Nucleic Acids

Research (1982) 10, 6487-6500; Wang, A. et al., Science 224, 1431-1433; Dalbadie-McFarland, G. et al., Proc. Natl. Acad. Sci USA (1982) 79, 6409-6413)."

(3) "Examples of TABI proteins include a TABI fusion protein that binds TAKI and includes the C-terminal 68 amino acid residues of TABI fused with the transcription activation domain of VP16 (Reference Example 1 of the specification at page 54, line 1). The specification also teaches a TABI that includes a complete TABI as shown in SEQ ID NO:4 (page 10, lines 14 to 16), TABI with amino acids 437-504 of SEQ ID NO:4 (page 11, lines 7 to 9), and SEQ ID NO:4 in which Arg is substituted for Ser at amino acid 52 (page 11, lines 21 to 25). Additional information regarding TABI proteins is provided in the specification at page 11, line 7, to page 12, line 9.

These arguments are not found to be persuasive for the following reasons.

(1) It is acknowledged that Example 1 of the specification (page 54, line 1) discloses a TABI fusion protein that includes the C-terminal 68 amino acid residues of TABI fused with the transcription activation domain of VP16. Said TABI fusion protein is encompassed by the genus of TABI proteins recited by Claims 2-11, 27, and 41-60 and is the sole example of a species encompassed by said genus. The other specific examples of TAB 1 proteins provided in the specification at page 8, line 29, to page 9, line 2 and page 9, lines 10 to 35 and set forth in the specification at page 1 1, line 7, to page 12, line 9 are not encompassed by the recited genus of TAB1 variants having 1-20 or 1-10 residue alterations in residues 437-504 of SEQ ID NO: 4 or variants wherein the polynucleotide encoding the variant hybridizes under high stringency conditions to SEQ ID NO: 1. Said examples do not teach how to make and use, without undue experimentation, said genus of TAB1 variants in the recited methods.

(2) The argument, based on the teachings of Bowie et al., 1990; Mark, D. F. et al., Proc. Natl. Acad. Sci. USA (1984) 81, 5662-5666; Zoller, M. J. & Smith, M. Nucleic Acids Research (1982) 10, 6487-6500; Wang, A. et al., Science 224, 1431-1433; Dalbadie-McFarland, G. et al., Proc. Natl. Acad. Sci USA (1982) 79, 6409-6413, that proteins are tolerant to changes in their amino acid residues is not persuasive. Even a single amino acid residue change can have a dramatic effect on the function of a protein (Witkowski et al, 1999 or Wishart et al, 1995). Without teaching which residues of 437-504 of SEQ ID NO: 4 are tolerant to change, and the level of tolerance, while maintaining the function of TAB1, determining which TAB1 variants can be used in the recite methods represents undue experimentation.

(3) See the reply to point (1).

For these reasons, rejection of Claims 2-11 and 27 under 35 U.S.C. 112, first paragraph is maintained, while new Claims 41-60 are hereby rejected under 35 U.S.C. 112, first paragraph.

Rejection of Claims 2-11, 27, under 35 U.S.C. 112, first paragraph for insufficient written description is maintained, and new Claims 41-47, 49, 50, and 54-60 are rejected under 35 U.S.C. 112, first paragraph for insufficient written description, because said claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to methods using a genus of TAB1 variants derived from residues 437-504 of SEQ ID NO: 4 having binding activity with TAK1. The specification teaches the structure of only a single TAB1 molecule that is a representative species of said genus. Moreover, the specification fails to describe any other representative species of TAB1 by any identifying characteristics or properties other than the

functionality of binding with TAK1. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Rejection of Claims 2-11, 27, under 35 U.S.C. 112, first paragraph for insufficient written description is maintained, and new Claims 41-60 are rejected under 35 U.S.C. 112, first paragraph for insufficient written description, because said claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to methods for testing the effect of inhibitors of TAK1/TAB1 binding on expression of inflammatory cytokines in response to a genus of activators. The specification teaches the structure of only a single activator that is a representative species of said genus. Moreover, the specification fails to describe any other representative species of activators by any identifying characteristics or properties other than the functionality of being inhibited by agents that block TAK1/TAB1 binding. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

In support of their request for withdrawal of the rejection of Claims 1-11 and 27 under 35 U.S.C. 112, first paragraph, for lack of enablement, applicants provide the following arguments, which are also relevant to new Claims 41-47, 49, 50, and 54-60.

(1) "...applicants have amended the independent claims to provide more explicit descriptions of both structure and function of the TAKI and TABI utilized in the claimed methods."

"This type of language [number of allowed residues to be substituted, deleted, and/or added-Examiner's insertion] is even more precise than the "percent homology" language explicitly permitted in Example 16 of the Synopsis of Application Written Description Guidelines (the "Synopsis").... The same rationale applies to the written description provided for TABI as presently limited in the independent claims (e.g., in categories (iv)-(vi) of claims 41...."

(2) "The specification also teaches specific examples of ... TABI proteins."

"Examples of TABI proteins include a TABI fusion protein that binds TAKI and includes the C-terminal 68 amino acid residues of TABI fused with the transcription activation domain of VP16 (Reference Example 1 of the specification at page 54, line 1). The specification also teaches a TABI that includes a complete TAB 1 as shown in SEQ ID NO:4 (page 10, lines 14 to 16), TAB 1 with amino acids 437-504 of SEQ ID NO:4 (page 11, lines 7 to 9), and SEQ ID NO:4 in which Arg is substituted for Ser at amino acid 52 (page 11, lines 21 to 25). Additional information regarding TABI proteins is provided in the specification at page 11, line 7, to page 12, line 9."

(3) Finally, applicants remind the Examiner that the present claims are drawn to methods, not compositions of matter. Courts have never required that all reagents specified in a method claim be described at the same level of specificity as the compositions claimed in a composition of matter claim. Accordingly, applicants request withdrawal of the rejection related to lack of written description.

These arguments are not found to be persuasive for the following reasons.

(1) It is acknowledged that applicants have amended the claims to recite methods of using a genus of TAB1 molecules having more limited number of structures, as set forth in categories (iv)-(vi) in Claim 41.... However, the genus of TAB1 molecules recited is not adequately described by the specification. Claim 41 (v) and 49 recite "wherein TAB1 of (a)... comprises amino acids 437-504 of SEQ ID NO: 4, with one to twenty amino acids substituted, deleted, and/or added". The genus of TAB1 molecules recited by Claims 41(v) and 49 encompasses molecules having as little as 70% homology to residues 437-504 of SEQ ID NO: 4. Likewise, Claim 50 recites "wherein TAB1 of (a)... comprises amino acids 437-504 of SEQ ID NO: 4, with one to ten amino acids substituted, deleted, and/or added", encompassing variants having as little as 85% homology. Said genera are large and variable genera of molecules, many of which will not bind TAK1. The specification fails to adequately describe which of the small number of variants, derived from residues 437-504 of SEQ ID NO: 4, or any characteristics of said variants other than the ability to bind TAK1, that can be used successfully. Therefore, a skilled artisan would not recognize that applicants were in possession of the claimed invention.

(2) It is acknowledged that the specification provides examples of TAB1 molecules that can be used in the recited methods. However, only one of said examples, the C-terminal 68 amino acid residues of TAB1 fused with the transcription activation domain of VP16, is an example of a variant having additions to residues 437-504 of SEQ ID NO: 4. No examples are given in which any residues of 437-504 of SEQ ID NO: 4 are substituted and/or deleted. Thus, the specification fails to provide examples, derived from residues 437-504 of SEQ ID NO: 4 and having 1-20 or 1-10 amino acids substituted and/or deleted, as recited in Claims 41, 49, and 50. Given this lack

of description of representative species, a skilled artisan would not recognize that applicants were in possession of the claimed invention.

(3) Methods claims using standard, well-known procedures that are accepted in the art as being routine do not require specific description. For example, methods for preparation of a recombinant protein, including recombinant TAK1 or TAB1, do not need to be described. However, the instant invention recites specific methods for testing the ability of a compound to inhibit TAK1 and TAB1 binding. To be adequately described, the specification should disclose a description of the TAK1 and TAB1 molecules to be used.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claims 2-11 and 27 under 35 U.S.C. 103(a) is maintained, while new Claims 41-59 are hereby rejected under 35 U.S.C. 103(a).

Claims 2-11, 27, 41, 42, and 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 in view of McCartney-Francis et al, 1998, Letterio et al, 1998, and Maeda et al, 1995. Shibuya et al teaches that TAB1 and TAK1 directly interact, as demonstrated using the yeast two-hybrid system (Fig 1), by coimmunoprecipitation (Fig 3), and in a luciferase-reporter expression system (Fig 4). A dominant negative TAK1, [$K^{63}W$]TAK1, blocks this interaction (Fig 4A). Shiguya et al also teach that residues 437-504 of TAB1 are sufficient for binding to TAK1 (pg 1181, parg 3, lines 1-3). Furthermore, a fragment of TAK1

consisting of residues 1-303 can bind TAB1, while fragments consisting of residues 1-76 or 214-579 cannot (Fig 1). Based on these latter results, a person of ordinary skill in the art would predict that residues 76-303 of TAK1 are sufficient for binding of TAB1. Shiguya et al further teach that inhibition of TAK1/TAB1 binding blocks a transcriptional response to TGF-β (Fig 4A). Therefore, Shiguya et al teach a screening method for identifying inhibitors of TAK1/TAB1 binding, that residues 437-504 of TAB1 and residues 76-303 of TAK1 are sufficient for said binding, and that said binding mediates the response to TGF-β. Shiguya et al do not teach testing a compound that inhibits TAK1/TAB1 binding for inhibiting expression of inflammatory cytokines. However, it is known in the art that TGF-β stimulates the expression of IL-1, IL-6, and TNF (as reviewed by McCartney-Francis et al, 1998/pg 565, parg 2, lines 1-5 and parg 3, lines 9-11 and Letterio et al, 1998/pg 147, parg 4, line 7-pg 148, line 1) as well as IL-10 (Maeda et al, 1995; Fig 7B). Therefore, it would be obvious to a person of ordinary skill in the art to test any compound that inhibits TAK1/TAB1 binding for inhibiting TGF-β-induced expression of IL-1, IL-6, IL-10, and TNF. Motivation to use the methods of Shiguya et al to test for additional inhibitors of TAK1/TAB1 binding and to test any compounds that inhibit binding for their effect on production of inflammatory cytokines is provided by the desire to identify said inhibitors, which may be useful as pharmaceutical agents. The expectation of success is high, as binding between TAK1 and TAB1 has been demonstrated and analysis for the production of inflammatory cytokines is known in the art. Therefore, Claims 2-11, 27, 41, 42, and 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 in view of McCartney-Francis et al, 1998, Letterio et al, 1998, and Maeda et al, 1995.

Claims 43-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 in view of McCartney-Francis et al, 1998, Letterio et al, 1998, and Maeda et al, 1995 and further in view of Wells et al, 1996. The teachings of Shibuya et al, 1996, McCartney-Francis et al, 1998, Letterio et al, 1998, and Maeda et al, 1995 are described above. The combination of Shibuya et al, 1996, McCartney-Francis et al, 1998, Letterio et al, 1998, and Maeda et al, 1995 do not teach using TAK1 variants derived from residues 76-303 of SEQ ID NO: 4 and TAB1 variants derived from 437-504 of SEQ ID NO: 4 in a binding reaction to test compounds for inhibition of TAK1/TAB1 binding. However, it is common in the art to make and use peptide variants in binding reactions (Wells et al, 1996). A person of ordinary skill in the art would be motivated to use TAK1 and TAB1 variants in a binding reaction to learn which residues of TAK1 and TAB1 are important for binding; such information would be important for molecular modeling of potential inhibitors of said binding. The expectation of success is high, as production of peptide variants using recombinant technology is common in the art. Therefore, Claims 43-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 in view of McCartney-Francis et al, 1998, Letterio et al, 1998, and Maeda et al, 1995 and further in view of Wells et al, 1996.

In support of their request for withdrawal of the rejection of Claims 1-11 and 27 under 35 U.S.C. 103(a), applicants provide the following arguments, which are also relevant to new Claims 41-60.

(1) "TGF-β is not an inflammatory cytokine. Neither Matsuomoto et al. nor a combination of Shibuya et al. and Metzler et al. discloses a relationship between (a) binding of TAKI to TABI and (b) inflammation, as required by each of the present claims. More specifically, these

references do not suggest any reason to first select a compound that inhibits TAKI/TABI binding and then... test the compound in an assay for inhibition of inflammatory cytokine expression (claims 41 and 63).... ... Thus, the primary references do not provide the motivation necessary to render the presently amended claims obvious."

(2) "None of the secondary references cited, even taken in combination, provides what is lacking in the primary references. Ausbel (1996), Palaparti et al. (1997), Swope et al. (1994), and Fields et al. (1989) were cited for their disclosures of particular assay techniques specified in dependent claims 2-1 1. None of these secondary references even mentions TAKI/TAB 1 binding, much less links it to inflammatory processes or suggests that an inhibitor of such binding would inhibit inflammatory cytokine expression or activity. Accordingly, no combination of the references cited by the Examiner teaches or suggests the claimed invention."

(3) "Applicants note that claim 27, as amended, now depends from claim 41 and so incorporates the limitations of claim 41. Claim 41 specifies a screening method that includes a step of assaying for inflammatory cytokine expression. As discussed above, Shibuya et al. and Matsuomoto et al. are both concerned with signal transduction triggered by TGF-β, which is not a pro-inflammatory cytokine. Neither of these references suggests that an inhibitor of TGF-β signal tranduction might be found to inhibit expression of inflammatory cytokines. Thus, there would have been no reason, based on the teachings of these references regarding the role of TABI and/or TAKI in TGF-P signal transduction, to identify an inhibitor of TAKI/TABI binding and then test the inhibitor to determine whether it inhibits expression of an inflâmmatory cytokine, as required by claims 41 and 27.

(4) Shirakabe does not provide the necessary motivation or expectation of success missing from the primary references. A mere disclosure that TAKI kinase activity can be induced by addition of 1L-1 does not suggest that TAB 1 binding is involved in this induction, nor that the TAKI activity induced by 1L-1 is linked to expression of inflammatory cytokines. Without this insight, there would have been no reason to carry out the screening method set forth in claims 41 and 27, as amended."

These arguments are not found to be persuasive for the following reasons.

(1) TGF-β can function as an inflammatory cytokine, inducing the production of Il-1, Il-6, and TNF (as reviewed by McCartney-Francis et al, 1998 and Letterio et al, 1998). Shibuya et al state that, "To analyze the TAK1-dependent pathway that functions in TGF-β signal transduction, we used the yeast two-hybrid system to search for proteins that directly interact with TAK1." (page 1179, parg 2) and "Thus, TAB1 may be an important signaling intermediate between TGF-β receptors and the TAK1 MAPKKK." (page 1181, last sentence). Therefore, it was known in the art, at the time of filing of the application herein, that TAB1 mediates activation of TAK1 by TGF-β by binding directly to TAK1. Based on these teachings, a person of ordinary skill in the art would predict that activation of TAK1 by binding of TAB1 in response to TGF-β would mediate the proinflammatory effects of TGF-β. Shibuya et al, 1996 further teach that inhibition of TAK1/TAB1 binding blocks a transcriptional response to TGF-β (Fig 4A). Therefore, a person of ordinary skill in the art would predict that inhibition of TAK1/TAB1 binding would block TGF-β-induced production of inflammatory cytokines.

(2) It is acknowledged that the secondary references do not mention TAK1/TAB1 binding. As stated by applicants, said references were cited for their disclosures of particular assay

techniques specified in the dependent claims. The secondary references are used only as evidence that said techniques are common in the art.

(3) See the response in (1).

(4) It is acknowledged that Shirakabe does not provide the necessary motivation or expectation of success for testing an inhibotor of TAK1/TAB1 binding for inhibition of IL-1- or TNF-induced activation of inflammatory cytokines and the mere disclosure that TAKI kinase activity can be induced by addition of IL-1 does not suggest that TAB 1 binding is involved in this induction, nor that the TAKI activity induced by IL-1 is linked to expression of inflammatory cytokines. In fact, Shirakabe et al teaches that an inhibitor of TAK1/TAB1 binding does not affect IL-1- or TNF-induced activation of TAK1 (pg 8143, parg 3, lines 7-12). Thus, as pointed out by applicants, there would be no reason to carry out the screening method set forth in the Claim 60. These issues are further addressed above under the USC 35 First Paragraph rejection of Claims 2-11, 27, and 41-60 for lack of enablement. However, Shirakabe et al, as discussed above, clearly do provide motivation and an expectation of success for testing an inhibitor of TAK1/TAB1 binding for inhibition of TGF-β-induced activation of the inflammatory cytokines IL-1, TNF, IL-6, and IL-10, as recited in the rejected claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.